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# CHAPTER

# 4

## **EPIDEMIOLOGY OF SEPSIS AND ITS RECOGNITION BY EMERGENCY MEDICAL SERVICE (EMS) PERSONNEL IN THE NETHERLANDS**

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## ABSTRACT

### Introduction

Little is known about the epidemiology of sepsis in the Netherlands. In addition, information regarding the ability of emergency medical service (EMS) personnel to recognize sepsis is lacking. The aim of this study is to determine epidemiological characteristics of sepsis and the recognition of sepsis by EMS personnel in an urban area in the Netherlands.

### Methods

A retrospective cohort study using transport information from EMS Amsterdam and admission diagnoses at the ED gathered through discharge data from two academic hospitals in Amsterdam for the year 2012.

### Results

253 patients with sepsis were evaluated, of which 131 were transported by ambulance. The in-hospital mortality rate of the total population was 21% and a mean length of hospital stay was of 13.5 days. 67 patients (26.5%) were admitted to the ICU. Almost half of the patients were assigned to the internal medicine ward (117; 46.2%). The most common site of infection was the urinary tract (30%). *E. coli* was the most frequent cause of infections. EMS staff recognized 18/131 (13.7%) transported patients with (severe) sepsis or septic shock. In 52 cases (39.7%) sepsis went unrecognized, probably due to an incomplete primary survey. In 60 cases (45.8%) sepsis went unrecognized, although enough SIRS criteria were present at initial presentation.

### Conclusion

Recognition of sepsis by EMS staff in the Netherlands is low, probably due to a lack of awareness of the syndrome and infrequent measurement of temperature and respiratory rate. As early initiation of treatment is crucial, the EMS staff, general practitioners and other specialties could benefit from more education on this critical illness.

## INTRODUCTION

Sepsis is a serious healthcare issue, with a high morbidity and mortality. American studies have revealed a mortality rate of 19.6% (1) which is nearly double the death rate of acute myocardial infarction and stroke (2). The worldwide incidence of sepsis was estimated at 19 million per year (3) and American studies report an incidence of 240.4 cases per 100,000 per year (1). For the Netherlands, the estimated incidence is 0,6 per 1000 Dutch inhabitants per year, which equals approximately 9000 patients per year (4). The incidence of sepsis is rising, which is thought to be due to several mechanisms. Firstly, the growing use of chemo- and immunotherapy which leaves patients with an inadequate immune system. Secondly, the rapid rise in antibiotic-resistant microorganisms. And finally, the ageing population which is at risk because of their numerous comorbidities (1). Most data on the epidemiological characteristics of sepsis have been derived from American studies. However, these data cannot be directly extrapolated to European health care systems. Moreover, part of the epidemiological findings originate from research performed in intensive care units (ICUs) and are therefore not applicable to the prehospital setting, emergency department (ED) and general hospital ward. Hence, one of the aims of this study was to determine the epidemiology of sepsis in an urban European region.

Many studies have revealed the paramount importance of the early recognition of sepsis by EMS staff, since it leads to early initiation of adequate therapy in the ED (5, 6), which can eventually lead to significant reductions in mortality, hospital length of stay and total costs (7, 8). In the US over 40% of all severe sepsis hospitalizations arrive at the emergency department (ED) by EMS transport (2). Approximately 3.3 per 100 emergency medical service (EMS) encounters in the US concerns patients with severe sepsis. This exceeds the figures for better known medical emergencies such as acute myocardial infarction (2.3 per 100 EMS) or stroke (2.2 per 100 EMS) (5).

Although recognition of septic patients by EMS staff is of significant importance, the actual rate of recognition seems low. Only 10.8% of the septic patients were recognized as such in a Dutch study which included patients transported by EMS and presented to the department of internal medicine (9). Sepsis, however affects patients from other specialties as well. Therefore the second goal of this study was to evaluate the recognition of all septic patients presented to different specialties by EMS personnel.

## METHODS

### Design and setting

We performed a retrospective cohort study of patients transported by EMS Ambulance Amsterdam in the year 2012. EMS Ambulance Amsterdam covers one of the largest EMS districts in the Netherlands and is responsible for approximately 110,000 transports per year. EMS Ambulance Amsterdam serves all seven hospitals in Amsterdam, two of which are tertiary care hospitals. EMS staff in the Netherlands are nurses specifically trained to diagnose and treat critical conditions. Most of these have more than 10 years of work

experience in the fields of critical care or emergency medicine (10). Detailed information of all patients presenting with sepsis in 2012 to the two academic tertiary care hospitals (VUMc and AMC) was collected in order to complement the data from the EMS.

## Study population

To qualify for inclusion in this retrospective study, patients had to be at least 18 years old and have the diagnosis sepsis, severe sepsis or septic shock.

The current international criteria from the SCCM/ESICM/ATS/SIS International sepsis definitions conference (11) were used. According to these criteria, the diagnosis sepsis should be considered when there is a proven or suspected infection in combination with two or more symptoms that suggest a systemic inflammatory response syndrome (SIRS), such as a heart rate more than 90/min, a respiratory rate more than 20/min or pCO<sub>2</sub> less than 4.3 kPa, a temperature less than 36.0°C or more than 38.3°C or leukocytes less than  $4 \times 10^9/l$ , more than  $12 \times 10^9/l$  or more than 10% leucocyte bands.

To meet the criteria for sepsis, a complete primary survey had to be performed to find out whether a patient had any of the above-described SIRS criteria.

Therefore, the number of EMS rides in which all vital parameters were registered was measured. The registered parameters were checked for compatibility with a diagnosis of sepsis according to SCCM/ESICM/ATS/SIS criteria.

If, during the study period in 2012, a patient with sepsis was registered in a hospital ward more than once, the patient was included each time. Yet if readmission occurred within 28 days after discharge, exclusion followed, because the readmission was most likely related to the previous disease episode.

The Medical Ethical Committee of the hospital approved the study, informed consent was waived as routine care was not influenced and no therapeutic intervention was performed.

## Cohort formation

The EMS database of Ambulance Amsterdam of the year 2012 was searched with the following search terms: infection, sepsis, 'severe sepsis', 'septic shock' to find all patients who were diagnosed and documented with any form of sepsis by EMS staff. All EMS forms were included in which sepsis, severe sepsis or septic shock was registered as definite diagnosis, secondary diagnosis, or mentioned as a comment or as information given by the emergency medical dispatch center.

The obtained data from the EMS were compared with data gathered from medical discharge records from the two academic hospitals. These records were scanned to find all patients who had an admission diagnosis of sepsis in the ED in the year 2012. Patients who developed sepsis in the hospital were excluded. When there was doubt concerning the diagnosis of sepsis, partly because some symptoms could likely be caused by illnesses other than infection or SIRS, expert advice was obtained from two independent physicians (internal medicine and infectious diseases) with more than 10 years of clinical experience.

To construct a patient database with the hospital data, the ninth revision of International Classification of Diseases and Related Health Problems (ICD-9) or Dutch Diagnosis and treatment (DTC) codes for (severe) sepsis or septic shock were used. A complete list of codes used is included in the appendix. From this database demographic information was gathered and mortality rate and length of stay at an intensive care unit or general ward were calculated. We also described the causative infective agents and the percentage of cultures that eventually became positive.

## STATISTICAL ANALYSIS

For data collection and analysis SPSS (IBM SPSS Statistics 20.0) was used. Population characteristics were summarized into descriptive statistics (mean, interquartile ranges). To compare categorical data Chi-square tests were used. When differences in means in different groups were to be evaluated, one-way ANOVA tests were used. To calculate survival, Kaplan Meier curves were made and log rank test was performed followed by Bonferroni post hoc analyses to determine the contribution of certain factors on survival. A  $p < 0.05$  was regarded as statistically significant.

## RESULTS

### Patient population

According to the discharge records of both hospitals, there were 466 patient records which were labeled with ICD-9 or DTC codes for sepsis. Of these, 213 (45.7%) records could not be included for the following reasons; 23.6% ( $n=110$ ) because sepsis was not the primary reason for visiting the ED and developed during hospitalization, 11.3% ( $n=53$ ) were excluded because they were merely patient transports from other hospitals and diagnosis was already known prior to transport, 16% ( $n=34$ ) because there was no detailed discharge data available. In 20 cases there was doubt about the diagnosis sepsis, for which expert physicians were asked to revise the cases. 16 of these cases were given a different diagnosis after expert-evaluation, see figure 1.

### Demographic characteristics

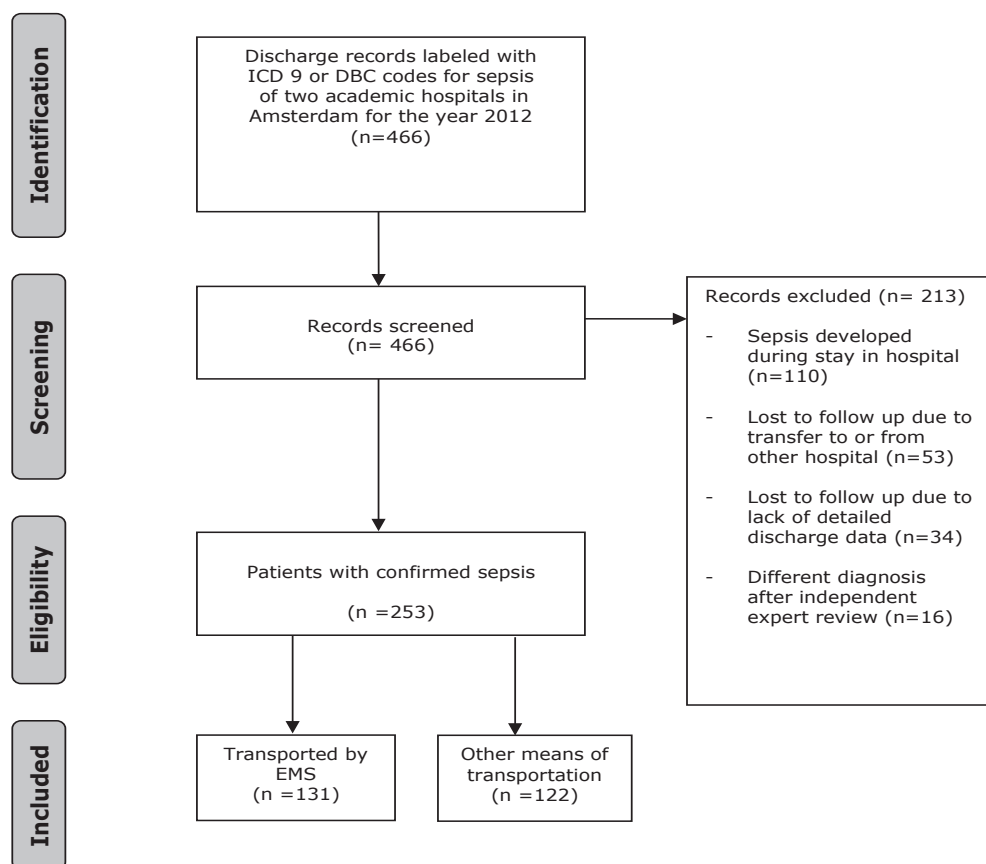
Among 253 patients with confirmed (severe) sepsis or septic shock the mean age was  $65.6 \pm 17.5$  years and 56.5% were male. In 80.6% of patients at least one coexisting condition was present, of which neoplasms (31.6%) and hypertension (25.3%) were most frequently documented. Forty-four (17.4%) patients used immunosuppressants at time of diagnosis (table 1).

### Clinical characteristics

Almost half of all the patients were assigned to internal medicine (117; 46.2%), the remaining patients were assigned to one of eleven other specialties. The median length of hospital stay was 8 days (range 0-69), 67 patients (26.5%) were admitted to the ICU and their median length of stay in the ICU was 4 days (range 0-39).

When categorizing all patients by severity of sepsis, 103 (4.7%) patients were categorized as having sepsis, 98 (38.7%) had severe sepsis, and 52 (20.6%) presented with septic shock. Patients with chronic heart disease were more likely to have severe sepsis and septic shock ( $p=0.031$ ). Patients with cancer were more likely to be categorized as having sepsis instead of severe sepsis or septic shock ( $p=0.035$ ).

A total of 53 patients (20.9%) died in the hospital as a consequence of sepsis. Moreover, after one year of follow up 31 more patients died, which makes all-cause mortality after one year follow up 32.3%. Patients who were transported by EMS were more likely to have severe sepsis ( $p=0.001$ ) and had a higher mortality (2.5 vs 14.8%) ( $p=0.046$ ). Patients who were known to have chronic heart disease ( $p=0.028$ ) and cancer ( $p=0.003$ ) were also more likely to die after an episode of sepsis. The mean age of patients who died of sepsis was higher than of patients who were still alive after one year of follow-up (71 vs. 63.4,  $p=0.013$ ). A majority of people who did not survive had been admitted to the ICU ( $p=0.001$ ). All clinical characteristics are listed in table 2.



**Figure 1.** Flowchart of study population

**Table 1.** Baseline characteristics for all patients (n=253)

	(n= %)
Age (SD)	65,6 ±17,5
Gender (% male)	143 (56.6)
Any co-existing conditions (%)	204 (80.6)
History of cancer (%)	80 (31.6)
Hypertension (%)	64 (25.3)
Chronic renal disease (%)	46 (18.2)
Diabetes mellitus (%)	44 (17.4)
Neurological diseases (%)	40 (15.8)
Peripheral vascular disease (%)	38 (15.0)
Chronic heart disease (%)	34 (13.4)
Chronic obstructive pulmonary disease (%)	26 (10.3)
Chronic liver disease (%)	23 (9.1)
HIV/Aids (%)	7 (2.8)
Other	
Use of immunosuppressants (%)	44 (17.4)
(functional) asplenic(%)	2 (0.8)
Morbid obesity (%)	2 (0.8)
IV drugs abuse (%)	2 (0.8)

**Table 2.** Clinical characteristics

	Means of transport		p- value
	EMS (n=131) n (%)	Other (n=122) n (%)	
Mortality	35 (26.7)	18 (14.8)	0.046
Length of hospital stay	14.92± 15.804	11.91 ±12.593	0.098
Number of ICU admissions	41 (31.3)	26 (21.3)	0.072
Length of stay at ICU	9.78± 8.912	5.85 ±6.792	0.059
Severity of sepsis:			0.001
Sepsis	41 (31.3)	62 (50.8)	
Severe sepsis	55 (42.0)	43 (35.2)	
Septic shock	35 (26.7)	17 (13.9)	

The most common site of infection was the urinary tract (30%) followed by the respiratory tract (17.4%). Patients with urinary tract infections, catheter infections, or infections of implanted medical devices were more likely to develop sepsis. Severe sepsis was seen more often in patients with an infection of the respiratory tract or abdominal cavity (p=.005).

### Recognition of sepsis by EMS personnel

In 2012 the EMS in the Netherlands transported a total number of 1.100.419 patients. 108.266 of these transports took place in Amsterdam, which accounts for almost 10% of



all transports. Our specific search in the ambulance database for the number of patients coded as being transported with (severe) sepsis or septic shock resulted in 123 transports, of which only 32 (26%) were destined for the two academic Amsterdam hospitals.

However, from the database formed by discharge records of the two tertiary centers in Amsterdam, 51.8% (n=131) patients were presented at the ED by ambulance. Referral of these patients was as follows: 61.8% (n=81) was seen by a general practitioner (GP) first, who then notified the EMS; 28.2% (n=37) patients called the EMS themselves, in the remaining cases EMS was notified by an extramural specialist (e.g. geriatric specialist, a local caregiver or the police (10%; n=13).

Almost half (44.8%, n=36) of the patients primarily seen by the GP had severe sepsis, however a third (33.3%; n=12) of these patients, as ordered by the GP, were transported at the lowest urgency level.

Patients who were seen by a general practitioner were more likely to be recognized as having sepsis by EMS staff (p=0.043).

EMS staff correctly diagnosed and documented 13.7% (n=18) patients with (severe) sepsis or septic shock in the ambulance. 45.8% (60/113) patients had sufficient SIRS-criteria and a suspected infection during ambulance transportation, but were not documented as septic.

Another 52 patients (39.7%) were septic at the moment of presentation at the ED, but had not been diagnosed in the ambulance and in addition an incomplete primary survey was documented by the ambulance personnel. Recognition of sepsis did not improve with increasing severity (p=0.924).

In 10 cases (7.6%) a complete primary survey was documented. Body temperature was the variable least documented (n=31; 23.6%), followed by respiratory rate (n=63, 48.1%) and blood pressure (n= 88; 67.2%) (table 3).

**Table 3.** Recognition of sepsis by EMS staff. Total n= 131 patients

	n (%)
Number of recognized septic patients	18 (13.7)
Number of missed diagnosis due to:	
Unknown reasons	60 (45.8)
Incomplete survey	52 (39.7)
Lack of diagnostic instruments (leukocyte count)	1 (0.8)
Number of completely documented primary surveys	10 ( 7.6)
Documented variables in primary survey	
Body temperature	31 (23.6)
Respiratory rate	63 (49.1)
Blood pressure	88 (66.2)
Glasgow coma scale	98 (74.8)
Heart rate	100 (76.3)

## DISCUSSION

From all patients with confirmed sepsis, more than half were transported by EMS. Of these, 61.8% were primarily evaluated by a general practitioner, before EMS personnel transported them. Sepsis was poorly diagnosed and documented by EMS personnel as well as GPs.

Almost half of the included patients with sepsis demonstrated physical signs of sepsis at time of evaluation by EMS staff, based on documented vital signs, yet a different diagnosis was documented. Another 39.7% of septic patients were not diagnosed and documented as such, and their primary survey was incomplete. Only 13.7% of the patients were diagnosed and documented by EMS personnel. Vital parameters were completely documented in only 7.6% of the ambulance forms, with body temperature and respiratory rate as parameters most frequently left out. The fact that body temperature was poorly assessed could be explained by the lack of tympanic thermometers. Till 2013 the Amsterdam ambulances were equipped with rectal thermometers, which are not the instruments of choice in the chaotic situations EMS personnel is often exposed to.

Sepsis remains a difficult disease to recognize, as the SIRS criteria can fit many other syndromes (e.g. pancreatitis, trauma), especially when there are no diagnostic laboratory tests available in the ambulance to meet the fourth SIRS criterion; white blood cell count. Still, a brief patient history combined with a simple primary survey of clinical parameters should enable the EMS staff to recognize most of the critically ill patients with sepsis (12).

It is possible that EMS personnel and GPs did recognize sepsis but failed to document it, as we only assessed the data derived from electronic or paper records. Valuable information may have been given verbally to the ED staff without seeing the need for proper documentation.

The response times in the Netherlands are approximately between 10-15 minutes (13). EMS personnel in the Netherlands often maintain the approach of “scoop and run”. Measuring and documenting vital parameters are deemed secondary. However suboptimal documentation may lead to information loss during handovers, which eventually can lead to insufficient care. The high rate of potentially missed diagnosis in combination with the importance of early recognition and initiation of treatment illustrate the need for education to raise the awareness about sepsis, the importance of a complete primary survey and structured communication and documentation (14). More focus should also be put on training EMS personnel to recognize different causes of critical illness, As some are difficult to identify due to a variability in clinical presentation (15, 16). Aside from EMS staff, general practitioners could also benefit from extra education.

The new national guidelines (17) for EMS personnel has incorporated the SBAR (situation, background, assessment, recommendation) method in order to improve handovers and decrease the chance of missing valuable information (18, 19). Together with screening tools, severity of the critical illness may be assessed in order to identify patients most at risk of deterioration. Simple to use scores such as the critical illness score or the EWS (17, 18) seem promising, but need validation before applying in the prehospital

setting. Using uniform screening tools and structured handovers by different healthcare providers throughout the acute care chain may improve patient safety through better communication and collaboration.

The population evaluated in this study corresponds with earlier studies with respect to age and sex (4, 20, 21). However when compared to earlier studies a larger proportion of our population had at least one co-existing condition. Especially cancer was reported more often (1, 22, 23). Moreover, a vast group of patients used immunosuppressants, which was not described before in other studies. This may be explained by the fact that our study focused on a specific population, namely that of tertiary care centers. Although, in accordance with previous studies (1, 2, 20), a mortality rate of 20.95% was found. More surprisingly, one year of follow up revealed an all-cause mortality of 33.3%. Although previous studies found high long term mortality rates as well (21, 24), the reason for the high mortality in our population is unclear. However a large percentage of cancer may be a possible explanation.

An infection of the respiratory tract is often described as the most frequent cause of severe sepsis (22, 25), but because our study also included patients with sepsis instead of severe sepsis and septic shock alone, our findings suggest, that at least in our population, urinary tract infections are more often responsible for sepsis (30.0% vs 17.4%).

There are several elements in this study that strongly contribute to its merit. Firstly, this study investigated the recognition of all patients with sepsis by EMS personnel, rather than those presented for internal medicine only at the ED. Secondly, the study demonstrated the importance of a complete primary survey for diagnosing sepsis.

Although conducted carefully, this study has its limitations. One of the aims of this study was to describe epidemiological characteristics of septic patients. Because of its design, using administrative data from academic hospitals to include patients, only a small sample of patients was found. The use of administrative data (ICD-coding) has been proven to be accurate, but is known for its tendency to underestimate the true incidence of sepsis (1, 26).

Our study population differed from previously described populations as we studied patients visiting tertiary care hospitals who are prone to have more malignancies and use more immunosuppressants. Therefore, epidemiological characteristics derived from this study cannot simply be extrapolated to all septic patients encountered in prehospital setting, emergency department (ED) and general hospital ward.

Early recognition and initiation of treatment may be the key to lower the mortality and morbidity of sepsis. The question is, whether it is possible to train EMS staff to recognize sepsis early and if this together with initiating early treatment indeed lowers the clinical outcomes in sepsis patients. EMS staff are often thought to be the first caregivers to arrive at a septic patient's bedside, but as seen in this cohort, general practitioners often precede. Future research such as the PHANTASi trial (27) which will investigate the effects of training the ambulance personnel to recognize suspected (severe) sepsis or septic shock together with early administration of antibiotics by EMS personnel may answer these important questions.

## CONCLUSION

Sepsis is a serious illness with high mortality and rising incidence. Patients are known to benefit from early initiation of treatment, but recognition in the prehospital setting by EMS as well as GPs is poor. Recognition of sepsis depends on the knowledge about the syndrome and the completeness of the primary survey. More attention should be given to education for care providers in the prehospital setting as well as towards raising awareness and sense of urgency for this potential lethal disease.

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